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Noninvasive Ventilation Improves Sleep in Amyotrophic Lateral Sclerosis: A Prospective Polysomnographic Study

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Study Objective: To evaluate the effects of noninvasive ventilation (NIV) on sleep in patients with amyotrophic lateral sclerosis (ALS) after meticulous titration with polysomnography (PSG).

Methods: In this prospective observational study, 24 ALS patients were admitted to the sleep laboratory during 4 nights for in-hospital NIV titration with PSG and nocturnal capnography. Questionnaires were used to assess subjective sleep quality and quality of life (QoL). Patients were readmitted after one month.

Results: In the total group, slow wave sleep and REM sleep increased and the arousal-awakening index improved. The group without bulbar involvement (non-bulbar) showed the same improvements, together with an increase in sleep efficiency. Nocturnal oxygen and carbon dioxide levels improved in the total and non-bulbar group. Except for oxygen saturation during REM sleep, no improvement in respiratory function or sleep structure was found in bulbar patients. However, these patients showed less room for improvement. Patient-reported outcomes showed improvement in sleep quality and QoL for the total and non-bulbar group, while bulbar patients only reported improvements in very few subscores.

Conclusions: This study shows an improvement of sleep architecture, carbon dioxide, and nocturnal oxygen saturation at the end of NIV titration and after one month of NIV in ALS patients. More studies are needed to identify the appropriate time to start NIV in bulbar patients. Our results suggest that accurate titration of NIV by PSG improves sleep quality.

Commentary: A commentary on this article appears in this issue on page 511.

Keywords: amyotrophic lateral sclerosis, noninvasive ventilation, sleep architecture, polysomnography

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily affecting the motor system and is characterized by progressive decrease in muscle strength. In addition to weakness of peripheral muscles, respiratory muscle weakness develops during the course of the disease, leading to reduced alveolar ventilation and respiratory failure, which is the main cause of death in ALS.[1,2]

A randomized controlled trial showed improvement in survival and quality of life (QoL) in ALS patients treated with noninvasive ventilation (NIV).[3] Although survival in the subgroup of patients with severe bulbar impairment did not improve, small improvements in QoL were observed.

Sleep is often disturbed in ALS patients.[4–7] In the presence of diaphragmatic dysfunction, REM sleep decreases.[8] Furthermore, sleep disturbances and nocturnal desaturations have been observed in ALS patients with normal respiratory function and preserved diaphragmatic innervation.[9]

Although NIV is predominantly used at night, few studies have examined the effect on sleep in ALS. Nevertheless, NIV could have a negative impact on sleep: wearing a mask and having air blown into the nose and/or mouth do not seem to create the perfect circumstances for good sleep quality. In the presence of weakness of facial or bulbar muscles, application of the mask could create difficulties, resulting in non-intentional leaks. Furthermore, difficulties with swallowing and managing secretions could interfere with NIV during sleep.[10] Conversely, improvement of oxygenation and carbon dioxide levels would have beneficial effects on sleep. Most studies dealing with sleep in ALS are based on patient-reported outcomes and reported improved sleep after NIV initiation.[3,11–14] Only two

BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous research has shown an improvement in survival and quality of life after initiation of NIV in ALS. Until now, no improvement in objective sleep parameters has been found; however, NIV was titrated during daytime. More detailed titration with polysomnography could perhaps improve quality of sleep.

Study Impact: This study shows that NIV titration with polysomnography improves objective sleep outcomes in ALS patients. Hence, meticulous titration of NIV has an important clinical impact in this patient group. Further research is necessary to create evidence to find the correct time to start NIV in bulbar ALS patients.

studies used polysomnography (PSG) to evaluate sleep during NIV and did not demonstrate improvement in sleep. Katzberg et al. showed an improved oxygenation but no improvement in sleep efficiency (SE), sleep arousals and sleep architecture during NIV.[15] Atkeson et al. showed a high frequency of patient-ventilator asynchronies (PVA).[16] Therefore, additional studies evaluating the effect of NIV on sleep are needed.[17]

The aim of this prospective study was to evaluate the influence of NIV on sleep in ALS by PSG with capnography before and after one month of NIV. Correlations were searched between therapeutic compliance with carbon dioxide measurement, improvement in patient-reported outcomes (total scores), and improvement in objective sleep parameters. Although a previous study shows no improvement in sleep structure,[15] we hypothesized that improvement in sleep structure could be found with a more meticulous NIV titration.

METHODS

Patients

At University Hospitals Leuven, ALS patients are routinely followed at the Neuromuscular Reference Centre (NMRC) in collaboration with pulmonologists (BB, DT). Patients with decreased inspiratory muscle strength (maximal inspiratory mouth pressure [MIP] < 60 cm H_2O), restrictive pulmonary function (vital capacity [VC] < 80% of the predicted value) and at least one of the following criteria were offered NIV: symptoms of nocturnal alveolar hypoventilation, increased daytime arterial carbon dioxide ([P_aCO_2] > 45 mm Hg) or an increase ≥ 10 mm Hg in transcutaneous carbon dioxide ($P_{tc}CO_2$) during sleep compared to their awake supine value (≥ 40 mm Hg). These inclusion criteria ensured that all patients in this study fulfilled the NIV criteria according to the guidelines of the American Academy of Neurology and the guidelines of the European Federation of Neurological Societies in ALS patients.[18,19]

Methods

Patients were admitted to the sleep lab for 5 days and 4 nights. Diagnostic PSG was performed on the first night. The next morning, NIV was started (Trilogy 100, Philips Respironics, Murrysville, PA, USA) with a nasal mask. Patients were accustomed to NIV in spontaneous (S) mode with an inspiratory positive airway pressure (IPAP) of 8 cm H_2O and an expiratory positive airway pressure (EPAP) of 4 cm H_2O. In the afternoon, IPAP was titrated in S mode during a nap to reach a tidal volume of 6 mL/min/kg ideal body weight. In the morning of days 3, 4, and 5, PSG was analyzed and NIV settings were adjusted according to nocturnal $P_{tc}CO_2$, oxygen saturation (SpO_2%), and occurrence of respiratory events. Each afternoon the patient napped for 1 hour to get accustomed to the new settings. In the presence of mouth leaks, a chin strap or oronasal mask was applied. After 1 month of NIV, patients were readmitted for PSG.

PSG (Medatec, Brainnet II, Brussels, Belgium) was used to record sleep and respiratory parameters. Sleep was scored and calculated after visual inspection of the tracings, according to the guidelines of the American Academy of Sleep Medicine (AASM) by 2 physicians with large experience in PSG analysis.[20] During diagnostic PSG, airflow was detected by a thermistor (Braebon, NY, USA) and nasal pressure cannula system (Teleflex Medical, NC, USA). A pneumotachograph (Hamilton Medical, Bonaduz, Switzerland) was used to record flow during NIV titration. Apnea and hypopnea were scored according to the AASM 2012 guidelines.[21] $P_{tc}CO_2$ was continuously monitored by a Tosca 500 monitor (Radiometer Ltd., Bronshoj, Denmark). The $P_{tc}CO_2$ and pneumotachograph data were incorporated in the PSG software and continuously followed.

Before and after 1 month of NIV, patients performed a VC measurement in sitting and (if possible) supine position according to the guidelines of the European Respiratory Society,[22] with prediction equations as proposed by Quanjer.[23] Daytime arterial blood gas (ABG) analysis was carried out in sitting position without ventilatory support. Measurements of MIP and sniff nasal inspiratory pressure (SNIP) were performed (MicroRPM, Micro Medical, Brooklyn, NY, USA).[24,25] Patients completed questionnaires concerning sleep, QoL, and functionality. The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) were used to measure sleep quality and daytime sleepiness, respectively.[26,27] Apart from the short-form 36 health questionnaire (SF-36), a generic measurement searching for health-related QoL,[28] we employed the McGill Quality of Life questionnaire (MQoL) measuring QoL specifically in patients with a life-threatening disease.[29] Functionality was measured by the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).[30] Bulbar function was based on the first 3 questions of the ALSFRS-R, and patients were classified as bulbar when this score was ≤ 9.[31]

This study was registered at clinicaltrials.gov (NCT01889043) and approved by the local ethical committee (ML7674). Written informed consent was obtained from all participants.

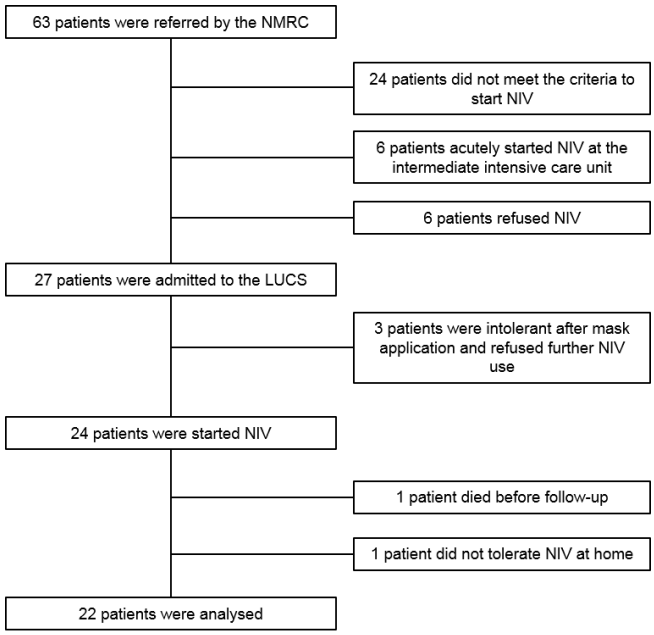
Statistical Analysis

Statistical analyses were performed with SAS 9.0 (SAS Institute Inc., Cary, NC, USA). Data are reported as mean ± standard deviation or as median and interquartile range. Comparisons between pre and post measurements were performed by paired t-test or Wilcoxon signed-rank test, depending whether data were normally distributed or not. Between-group comparisons were performed by unpaired t-test or Mann-Whitney test. Spearman rho and Pearson were used to test correlations. Results were considered significant when $p < 0.05$. Figures were made by GraphPad Prism 5.01 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

From January 2012 to April 2013, 63 patients were referred to our unit by the NMRC. Twenty-four patients (60 ± 10 years, 21 males) were started on NIV (**Figure 1**). Demographic data and baseline measurements of inspiratory muscle strength, VC, and ABG are shown in **Table 1**. Measurement of supine VC could not be performed in 7 patients because of severe orthopnea. Three patients refused ABG analysis, and 2 patients had problems performing MIP/SNIP measurement. The most prevalent symptoms of alveolar hypoventilation were orthopnea (20 patients), increased daytime sleepiness (17 patients),

Figure 1—Flow chart of patient inclusion.



NMRC, neuromuscular reference centre; NIV, noninvasive ventilation; LUCS, Leuven University Centre For Sleep/Wake Disorders.

Table 1—Demographic data and baseline measurements of arterial blood gases, vital capacity, and inspiratory muscle strength.

	All (n = 24)	Non-bulbar (n = 14)	Bulbar (n = 10)
Sex (male/female)	21/3	13/1	8/2
Age (years)	60 ± 10	61 ± 8	58 ± 13
Time from ALS symptom onset (months)	26 ± 13	27 ± 14	25 ± 12
Daytime P_aCO_2 (mm Hg)	46 ± 6	48 ± 6	42 ± 3*
Daytime P_aO_2 (mm Hg)	77 ± 12	72 ± 12	86 ± 7*
VC_{seat} (%pred)	56 ± 14	60 ± 16	51 ± 10
VC_{sup} (%pred)	41 ± 9	43 ± 11	38 ± 8
MIP (cm H_2O)	−35 ± 12	−38 ± 11	−30 ± 13
SNIP (cm H_2O)	−25 ± 21	−22 ± 26	−30 ± 11

Data are given as mean ± standard deviation. *$p < 0.05$ bulbar vs. non-bulbar. P_aCO_2, partial pressure of carbon dioxide in arterial blood; P_aO_2, partial pressure of oxygen in arterial blood; VC_{seat}, seated vital capacity; VC_{sup}, supine vital capacity; MIP, maximal inspiratory pressure; SNIP, sniff nasal inspiratory pressure.

frequent awakenings (15 patients), and exertional dyspnea (12 patients). In our group, 10 patients showed important bulbar involvement and were classified as "bulbar"; 14 patients were classified as "non-bulbar."

Seventeen patients were discharged from the hospital on spontaneous/timed (S/T) mode and 7 patients on S mode, due to intolerance of S/T mode (5 of these patients had bulbar involvement with residual saliva and swallowing problems which aggravated with the S/T mode and thereby influencing their subjective and objective sleep quality). Nineteen patients were ventilated by nasal mask and 5 patients by oronasal mask. IPAP was set at 14 ± 2 cm H_2O and EPAP was set at 4 ± 1 cm H_2O. Patients on S/T mode had a back-up frequency of 16 ± 2/min. One non-bulbar male patient died of pneumonia before follow-up, and one bulbar male patient could not be tested with NIV after one month because of intolerance (1.8 h/day use, only during daytime). These 2 patients were excluded from further analysis.

After one month (38 ± 9 days), ALSFRS-R was significantly decreased ($p < 0.01$ for all patients; $p < 0.05$ for non-bulbar patients or bulbar patients). Daytime P_aCO_2 decreased significantly in the total group (46 ± 6 vs. 43 ± 5 mm Hg, $p < 0.05$) and non-bulbar patients (48 ± 6 vs. 43 ± 5 mm Hg, $p < 0.05$).

Sleep Architecture

At baseline, PSG revealed poor sleep quality (**Table 2**). A low SE, with low percentages of slow wave sleep (N3) and REM sleep, and an increased arousal-awakening index (AAI) were present.[32] Sleep quality of bulbar patients was better than sleep quality of non-bulbar patients, with less stage 1 sleep (N1), more REM sleep, and a lower AAI. Except for one patient who had no N3, all sleep stages were present in bulbar patients, while N3 and REM sleep were absent in 8 and 5 non-bulbar patients, respectively.

After one month, several changes in sleep architecture were present. AAI and percentage of N1 sleep were significantly reduced and percentages of N3 and REM sleep were significantly increased (while total sleep time was not significantly higher) in all patients. The same observations were made in the group of non-bulbar patients, with even a significant increase in SE. In the non-bulbar group all sleep stages were now present in all patients but one. In the bulbar patients, no improvement in SE, sleep stages, or AAI was found (**Table 2**).

Analyzing PSG of the night with the final settings during the start-up procedure already found improvements in sleep structure compared to diagnostic PSG. The total group showed improvement in AAI (17 [12–21] per hour of sleep; $p < 0.01$) and the amount of N1 (4 [2–9] %; $p < 0.01$), N3 (19 [8–30] %; $p < 0.01$) and REM (21 [14–26] %; $p < 0.05$) sleep, while the non-bulbar group showed improvement in SE (81 [67–84] %; $p < 0.01$), AAI (18 [13–22] per hour of sleep; $p < 0.01$), and N1 (3 [2–9] %; $p < 0.01$), N3 (19 [4–30] %; $p < 0.05$), and REM (25 [20–29] %; $p < 0.01$) sleep. Bulbar patients showed no improvement at discharge.

Sleep Respiratory Parameters

At diagnostic PSG, patients showed few obstructive events (0.0 [0.0–0.3] obstructive apneas per hour of sleep; 0.1 [0.0–6.3] obstructive hypopneas per hour of sleep). **Table 3** shows improvements in SpO_2% and $P_{tc}CO_2$. In the total group the time spent with SpO_2% < 90% improved during the total night as well as in REM and N1 and stage 2 (N2) sleep. Time spent with $P_{tc}CO_2 > 55$ mm Hg improved during the total night measurement, N1, N2, and N3 sleep. Non-bulbar patients showed significant changes in the same parameters as the total group. Additionally, a trend to improvement was found for time spent with SpO_2% < 90% in N3 ($p = 0.0579$). Bulbar patients only

Table 2—Sleep structure in all, non-bulbar and bulbar patients before and after one month of NIV use.

	All (n = 22)		Non–bulbar (n = 13)		Bulbar (n = 9)	
	Pre	Post	Pre	Post	Pre	Post
TST (min)	317 (216–442)	351 (261–455)	311 (107–428)	364 (273–457)*	350 (287–454)	337 (241–436)
SE (%)	59 (40–72)	68 (50–80)	62 (19–81)	72 (52–85)*	59 (49–65)	68 (44–74)
N1 (%)	11 (6–32)	8 (4–14)*	23 (8–56)	5 (4–11)**	7 (5–13)#	9 (6–17)
N2 (%)	63 (37–75)	54 (46–63)	63 (36–77)	55 (49–63)	65 (42–75)	53 (33–64)
N3 (%)	1 (0–10)	15 (8–19)*	0 (0–6)	16 (13–19)*	7 (1–18)	12 (1–21)
REM (%)	9 (1–16)	18 (9–23)*	6 (0–12)	22 (10–23)**	17 (7–25)##	16 (9–23)
AAI (n/h)	37 (16–55)	17 (11–21)**	42 (36–82)	17 (12–26)**	16 (13–37)#	18 (11–20)

*p < 0.05 pre vs. post. **p < 0.01 pre vs. post. #p < 0.05 bulbar vs. non-bulbar. ##p < 0.01 bulbar vs. non-bulbar. TST, total sleep time; SE, sleep efficiency; N1, stage 1 sleep; N2, stage 2 sleep; N3, slow wave sleep; REM, rapid eye movement sleep; AAI, arousal-awakening index; pre, before NIV; post, after 1 month of NIV.

Table 3—Measurements of oxygen saturation and transcutaneous carbon dioxide measurements at baseline and after one month of NIV treatment.

	All (n = 22)		Non-bulbar (n = 13)		Bulbar (n = 9)	
	Pre	Post	Pre	Post	Pre	Post
SpO_2 total night < 90 (%)	11.1 (1.1–59.9)	0.8 (0–6.2)**	29.7 (3.7–98.0)	1.1 (0.2–100.0)**	6.4 (0.2–33.5)	0.0 (0.0–9.6)
SpO_2 REM < 90 (%)	35.3 (2.1–100.0)	0.5 (0.0–3.0)**	37.1 (12.6–100.0)	0.9 (0.0–7.1)*	33.4 (0.2–82.5)	0.1 (0.0–2.5)*
SpO_2 N3 < 90 (%)	8.3 (0.0–72.0)	0.0 (0.0–0.1)	57.3 (4.3–100.0)	0.0 (0.0–0.1)	1.8 (0.0–44.1)	0.0 (0.0–16.8)
SpO_2 N1+N2 < 90 (%)	10.4 (1.4–97.9)	0.0 (0.0–6.2)**	48.0 (2.3–99.1)	0.2 (0.0–7.7)**	7.7 (0.5–58.9)	0.0 (0.0–7.0)
$P_{tc}CO_2$ total night > 55 (%)	42.5 (0.1–95.4)	0.0 (0.0–5.7)**	78.7 (5.2–95.9)	0.0 (0.0–6.2)*	2.6 (0.0–76.1)	0.0 (0.0–5.2)
$P_{tc}CO_2$ REM > 55 (%)	0.8 (0.0–100.0)	0.0 (0.0–14.6)	52.8 (0.0–100.0)	0.0 (0.0–8.3)	0.0 (0.0–100.0)	0.0 (0.0–46.7)
$P_{tc}CO_2$ N3 > 55 (%)	55.8 (0.0–100.0)	0.0 (0.0–0.0)*	100.0 (75.0–100.0)	0.0 (0.0–0.0)*	0.0 (0.0–77.9)#	0.0 (0.0–0.0)
$P_{tc}CO_2$ N1+N2 > 55 (%)	50.3 (0.0–98.1)	0.0 (0.0–2.3)**	89.4 (0.0–98.9)	0.0 (0.0–1.1)*	2.2 (0.0–85.1)	0.0 (0.0–3.4)

Data are given as median (25^{th}–75^{th} percentile). *p < 0.05 pre vs. post. **p < 0.01 pre vs. post. #p < 0.05 bulbar vs. non-bulbar. SpO_2, oxygen saturation; $P_{tc}CO_2$, transcutaneous carbon dioxide; REM, rapid eye movement sleep; N3, slow wave sleep; N1+N2, stage 1 and 2 sleep; Pre, before NIV; post, after one month of NIV.

improved in time spent with SpO_2% < 90% in REM sleep. In the bulbar group, no changes were found in $P_{tc}CO_2$ measurement.

Analyzing the data of SpO_2% and $P_{tc}CO_2$ of the night with the final settings during titration showed improvements in comparison with the diagnostic PSG. The total group improved in the time spent with SpO_2% < 90% during the total night (4 [0–49] %; p < 0.01), N1+N2 (3 [0–48] %; p < 0.01), and REM (1 [0–50] %; p < 0.01) sleep, and also in time spent with $P_{tc}CO_2$ > 55 mm Hg during the total night (0 [0–21] %; p < 0.01) and N1+N2 sleep (20 [0–16] %; p < 0.05). The non-bulbar patients improved in time spent with SpO_2% < 90% during the total night (5 [1–61] %; p < 0.05), N1+N2 (4 [0–72] %; p < 0.05) and REM (2 [0–60] %; p < 0.05) sleep and time spent with $P_{tc}CO_2$ > 55 mm Hg during the total night (0 [0–17] %; p < 0.01) and N1+N2 (0 [0–14] %; p < 0.05) sleep, while bulbar patients only improved in the time spent with SpO_2% < 90% during REM sleep (1 [0–18] %; p < 0.05).

Questionnaires

Table 4 shows the data of the ESS, PSQI, and MQoL before and after one month of NIV. Non-bulbar patients showed improvements in daytime sleepiness (8.0 [3.5–11.5] vs 4.0 [3.0–7.0]; p < 0.05), the PSQI total score (8.0 [6.5–14.5] vs 5.0 [2.5–7.5]; p < 0.01), MQoL total score (5.0 [4.2–6.0] vs 6.8 [5.4–7.9]; p < 0.01), and several subscales. In contrast, bulbar patients only reported an improved PSQI total score (9.0 [6.5–12.5] vs 5.0 [4.0–9.0]; p < 0.01) and sleep duration (1.0 [0.0–2.0] vs 0.0 [0.0–0.5]; p < 0.01). Improvements were found in the SF-36 emotional health subscale for the total (50 [28–77] vs 62 [56–81]; p < 0.0001), non-bulbar (50 [29–84] vs 68 [54–90]; p < 0.01), and bulbar group (50 [25–67] vs 60 [56–77]; p < 0.01). Vitality changed only for the total (35 [10–50] vs 50 [29–60]; p < 0.05) and non-bulbar groups (25 [10–49] vs 48 [26–60]; p < 0.01).

Compliance

Therapeutic compliance was significantly correlated with initial daytime P_aCO_2 (**Figure 2A**). Furthermore, NIV use was correlated with baseline nocturnal $P_{tc}CO_2$ and changes in $P_{tc}CO_2$ measurements over 1 month (**Table 5**). **Figure 2B** shows a statistical significant relationship between compliance and change in MQoL total score in the total group and non-bulbar group. No correlation was found between therapeutic compliance and change in any objective sleep parameter.

DISCUSSION

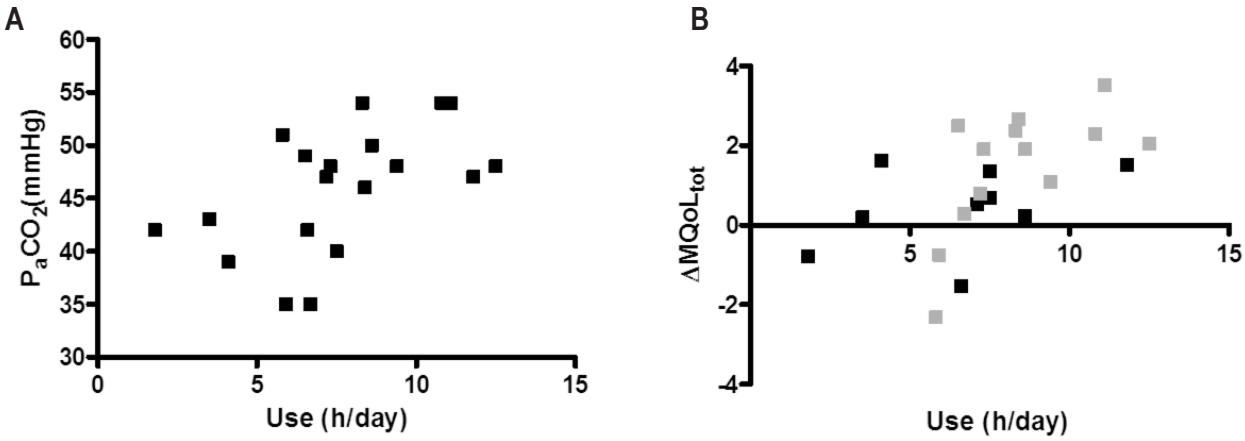
This is the first study demonstrating improvements in sleep architecture and respiratory parameters in ALS patients during treatment with nocturnal NIV, measured by PSG. The total

Table 4—Measurements of Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality index (PSQI), and McGill quality of life questionnaire (McGill) at baseline and after one month.

	All (n = 22)		Non-bulbar (n = 13)		Bulbar (n = 9)	
	Pre	Post	Pre	Post	Pre	Post
ESS	8.0 (3.8–10.0)	4.5 (3.0–7.3)*	8.0 (3.5–11.5)	4.0 (3.0–7.0)*	8.0 (2.5–9.5)	6.0 (2.5–9.0)
$PSQI_{tot}$	8.5 (6.8–13.3)	5.0 (3.0–8.3)**	8.0 (6.5–14.5)	5.0 (2.5–7.5)**	9.0 (6.5–12.5)	5.0 (4.0–9.0)**
$PSQI_{qual}$	1.5 (1.0–2.0)	1.0 (0.0–1.0)**	2.0 (1–2.5)	0.0 (0.0–1.0)**	1.0 (0.5–2.0)	1.0 (1.0–1.0)
$PSQI_{lat}$	1.0 (0.0–2.3)	0.5 (0.0–1.3)	0.0 (0.0–2.0)	0.0 (0.0–1.0)	2.0 (0.5–3.0)	1.0 (0.5–2.0)#
$PSQI_{dur}$	1.0 (0.0–2.0)	0.0 (0.0–0.0)**	1.0 (0.0–2.5)	0.0 (0.0–0.0)*	1.0 (0.0–2.0)	0.0 (0.0–0.5)**
$PSQI_{eff}$	2.0 (0.0–3.0)	0.0 (0.0–1.0)**	2.0 (0.0–3.0)	0.0 (0.0–0.5)*	2.0 (0.0–3.0)	0.0 (0.0–1.0)
$PSQI_{dist}$	1.0 (1.0–2.0)	1.0 (1.0–1.0)**	1.0 (1.0–2.0)	1.0 (1.0–1.0)**	1.0 (1.0–2.0)	1.0 (1.0–1.5)
$PSQI_{med}$	0.0 (0.0–3.0)	0.0 (0.0–2.3)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–2.5)	0.0 (0.0–0.5)
$PSQI_{dysf}$	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–1.5)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
$MQoL_{SIS}$	5.0 (3.0–7.0)	7.0 (4.8–7.0)	5.0 (2.5–7.0)	7.0 (4.5–8.0)*	5.0 (3.0–7.5)	5.0 (4.5–7.0)
$MQoL_{tot}$	5.1 (4.1–6.3)	6.3 (5.0–7.5)**	5.0 (4.2–6.0)	6.8 (5.4–7.9)**	5.9 (3.8–6.9)	6.1 (4.9–6.8)
$MQoL_{physsym}$	3.3 (1.8–5.4)	5.0 (3.7–7.5)*	2.7 (1.7–4.5)	5.3 (4.2–7.2)*	4.7 (2.2–7.0)	4.6 (2.5–8.7)
$MQoL_{physwb}$	4.0 (3.0–5.3)	5.0 (3.8–7.0)*	3.0 (3.0–4.5)	6.0 (4.5–7.0)*	5.0 (2.0–6.5)	4.0 (3.0–6.0)
$MQoL_{psysym}$	4.9 (2.5–7.0)	7.0 (5.3–8.5)*	3.8 (2.3–6.8)	7.3 (5.1–8.5)*	6.5 (3.6–7.7)	7.0 (5.1–8.3)
$MQoL_{exiwb}$	5.8 (4.2–6.8)	6.3 (4.6–7.6)	5.7 (3.7–6.9)	7.0 (3.5–8.3)	5.8 (4.2–6.8)	5.6 (5.2–6.5)
$MQoL_{supp}$	8.3 (6.8–10.0)	8.0 (6.9–9.5)	9.0 (7.3–10.0)	9.0 (7.8–9.8)	7.0 (5.0–9.3)#	7.0 (6.3–8.0)

Data are given as median (25^{th}–75^{th} percentile). *p < 0.05 pre vs. post. **p < 0.01 pre vs. post. #p < 0.05 bulbar vs. non-bulbar. ESS, Epworth Sleepiness Scale; $PSQI_{tot}$, Pittsburgh Sleep Quality index total score; $PSQI_{qual}$, sleep quality; $PSQI_{lat}$, sleep latency; $PSQI_{dur}$, sleep duration; $PSQI_{eff}$, sleep efficiency; $PSQI_{dist}$, sleep disturbances; $PSQI_{med}$, sleep medication; $PSQI_{dysf}$, sleep dysfunction; $MQoL_{SIS}$, McGill Quality of Life questionnaire single item scale; $MQoL_{tot}$, total score; $MQoL_{physsym}$, physical symptoms; $MQoL_{physwb}$, physical well-being; $MQoL_{psysym}$; psychological symptoms; $MQoL_{exiwb}$, existential well-being; $MQoL_{supp}$, support; Pre, before NIV; Post, after one month of NIV.

Figure 2—Correlation between therapeutic compliance and daytime arterial carbon dioxide before NIV and change in quality of life.



(A) Correlation between daytime arterial carbon dioxide (n = 19) before NIV initiation and use hours: r = 0.54, p < 0.05. **(B)** Correlation between change in the total score of the McGill questionnaire ($\Delta MQoL_{tot}$) and use hours in the total group (r = 0.56, p < 0.01) and non-bulbar group (gray dots) (r = 0.63, p < 0.05). P_aCO_2, partial pressure of carbon dioxide in arterial blood; $\Delta MQoL_{tot}$, change in the total score of the McGill Quality of Life questionnaire.

group and subgroup of non-bulbar patients showed improvements in SE, amount of N3 and REM sleep, AAI, and oxygenation and carbon dioxide levels present at the end of the titration procedure; these improvements remained after one month of NIV use. In addition, patients also reported better sleep with less somnolence during daytime and improvement in QoL. In bulbar patients, improvements were limited, with no change in sleep architecture, small improvement in nocturnal SpO_2%, and few subjective improvements.

In our study, NIV improved (apart from gas exchange) PSG-recorded and patient-reported sleep and QoL. Few studies showed improvement in sleep by patient-reported outcomes in ALS. Lyall et al. did not make a distinction between bulbar and non-bulbar patients, but VC in their patients was similar to our group. Without specifying time of follow-up, they found a significant improvement in ESS score.[12] Butz et al. showed a long-term improvement of sleep quality by using the PSQI, also without distinction between bulbar and non-bulbar

Table 5—Correlations of therapeutic compliance (use hours) with baseline measurements of time of transcutaneous carbon dioxide spent > 55 mm Hg and changes over one month in time of transcutaneous carbon dioxide spent > 55 mm Hg.

	Use Hours	
	r	p
$P_{tc}CO_2$ > 55 total night	0.68	0.0009
$P_{tc}CO_2$ > 55 REM	0.62	0.0084
$P_{tc}CO_2$ > 55 N3	0.70	0.0073
$P_{tc}CO_2$ > 55 N1+N2	0.70	0.0007
$\Delta P_{tc}CO_2$ > 55 REM	0.53	0.0365
$\Delta P_{tc}CO_2$ > 55 N3	0.73	0.0076
$\Delta P_{tc}CO_2$ > 55 N1+N2	0.61	0.0041

Δ, change over 1 month; $P_{tc}CO_2$, transcutaneous carbon dioxide; REM, rapid eye movement sleep; N3, slow wave sleep; N1+N2, stage 1 and 2 sleep

involvement.[11] In the randomized controlled trial, Bourke et al. used the symptom subscale of the Sleep Apnea Quality of Life Index (SAQLI) and found an improvement of symptoms in the total group and in patients with good bulbar function.[3] Patients with poor bulbar function had no improvement, except for the time-weighted mean of the SAQLI symptom score. Although our bulbar patients used NIV 6.4 h/day, compared to 3.8 h/day in the study of Bourke et al., we also found no significant changes in our bulbar group (PSG or patient-reported), except for the total PSQI score and its subscale of sleep duration.

To our knowledge, only one study evaluated PSG recorded sleep architecture in ALS patients on NIV.[15] Our results are in contrast with this study as it showed no change in SE, sleep arousals, or sleep architecture. Several factors could explain these differences. In Katzberg's study, NIV was titrated during daytime according to the patient's comfort. In our study, NIV was titrated by PSG guidance; hence, sleep structure was taken into account during titration. Furthermore, the NIV device itself could influence sleep due to possible differences in triggering. In our study, the Trilogy 100 was used with the AutoTrak setting. Katzberg et al. did not mention their trigger modality, but fixed trigger sensitivity could influence the number of PVAs and AAI, as trigger sensitivity could possibly differ between sleep stages.[33–36] Another difference is the use of average volume-assured pressure support (AVAPS) in Katzberg's study. Until now, no randomized controlled trial with AVAPS has been performed in ALS. Impact of self-changing pressures on leaks, PVA, and sleep is therefore unknown. Although in a heterogenic group of neuromuscular patients, volume-targeted ventilation has shown to cause more PVA than pressure support ventilation.[37] Katzberg et al. already suggested that an additional night of PSG to titrate NIV would have been helpful to optimize treatment in their cohort.[15] In stable neuromuscular patients, with at least 3 months of NIV use, 66% still showed a PSQI score ≥ 5 (mean score 6.98 ± 3.2).[38] In that study, NIV was established following evaluation of diurnal comfort, respiratory function, and gas exchange, and of nocturnal in-hospital cardiorespiratory polygraphic monitoring, but without any sleep study. As most patients still showed poor sleep quality, the authors stated that great care should be paid to an effective and optimal NIV setting. Indeed, as the median (interquartile range) PSQI score in our study before NIV was 8.5 (6.8–13.3) and decreased to 5.0 (3.0–8.3), with even a significant improvement in the bulbar patients, it seems that PSG could be of major importance to improve sleep quality in patients starting with NIV.

The most striking result of this study is that NIV improved PSG-recorded and patient-reported sleep, QoL, nocturnal SpO_2%, and carbon dioxide in the total and non-bulbar group of patients, but that almost no improvements were found in the group of bulbar patients. An explanation could be compiled from the data before NIV initiation; PSG recorded sleep quality, SpO_2%, and carbon dioxide measurements were better in the bulbar group and therefore, there is less room for improvement. The question then arises whether NIV is started too soon in bulbar patients, as also P_aCO_2 was lower and SNIP was slightly higher. These patients frequently complain of orthopnea but this sensation is probably partly induced by breathing difficulties due to accumulation of secretions and/or excessive saliva. On the other hand, postponing NIV in bulbar patients could impede NIV titration and adjustment to a mask secondary to advanced bulbar symptoms. This point of discussion becomes even more complicated if we consider our bulbar patients individually. Indeed, sleep and QoL did not improve in patients with a very low score on the bulbar questions of the ALSFRS-R, but patients with a score of 8 and 9 had variable results. It could be suggested that NIV should be initiated in patients with bulbar involvement when decreased sleep quality is reported by the patient or PSG, but certainly more research on when to start NIV in bulbar ALS patients is necessary.

Correlation was found between therapeutic compliance and nocturnal time spent above 55 mm Hg $P_{tc}CO_2$ at baseline. This is in agreement with Kim et al. who showed that duration of nocturnal hypercapnia, measured by end-tidal capnography, was predictive for good compliance.[39] This finding could promote early measurement of nocturnal $P_{tc}CO_2$, even in normocapnic patients during daytime, and together with the correlation between compliance and change of nocturnal $P_{tc}CO_2$, encourage good compliance. Even a simple daytime P_aCO_2 measurement was correlated with future compliance. Apparently, patients with high P_aCO_2 need less encouragement on their compliance, but patients with mild hypercapnia should be well observed to increase compliance. Our results show a positive correlation between change in QoL and therapeutic compliance in the total and non-bulbar groups. Bourke et al. also showed a strong relationship between QoL and NIV compliance, even over the long term.[13]

One limitation of our study is that patients during diagnostic PSG are exposed for the first time to PSG measurement, and that this could influence sleep negatively. However, after one month of sleeping with NIV at home, it will still be an adaptation when full PSG is carried out again, especially taking into account the increased functional disability. Another limitation is the limitation of our data to results after one month. Butz et al. showed that patient-reported improvements in sleep emerge after one month of NIV treatment and could last for up to 10 months.[11] As the goal of NIV is improving sleep and QoL and

simultaneously increasing survival, longitudinal studies on the effect of NIV on sleep and the effect of improved sleep quality on survival are definitely needed. We know that PSG is not routinely used during NIV titration in most countries. Probably, three nights of titration with PSG (as performed in this study) will not be necessary in most patients; however, the findings of this study underline the importance of PSG during NIV titration in patients with ALS.

CONCLUSIONS

This is the first prospective study showing objective improvement in different sleep parameters after one month of NIV in ALS. Increased amounts of N3 and REM sleep with a decreased AAI and improved gas exchange were observed, especially in patients with none or mild bulbar involvement. Furthermore, patients reported better sleep and QoL. In patients with severe bulbar involvement, almost no improvement was found, and additional research is needed on when NIV should be started in these patients. This study suggests that meticulous titration of NIV by PSG could improve sleep in patients with ALS.

ABBREVIATIONS

AAI, arousal-awakening index
ABG, arterial blood gas
ALS, amyotrophic lateral sclerosis
EPAP, expiratory positive airway pressure
MIP, maximal inspiratory mouth pressure
MQoL, McGill Quality of Life questionnaire
NIV, non-invasive ventilation
PSG- polysomnography
PSQI, Pittsburgh Sleep Quality Index
PVA, patient-ventilator asynchronies
QoL, quality of life
REM, rapid eye movement
SAQLI, Sleep Apnea Quality of Life Index
SE, sleep efficiency
SNIP, sniff nasal inspiratory pressure
VC, vital capacity

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DISCLOSURE STATEMENT

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